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WHO Report

WHO consultation on clinical evaluation of vaccines, 17–18 July 2014, WHO Headquarters, Geneva, Switzerland

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ABSTRACT

A World Health Organization (WHO) consultation on guidelines for National Regulatory Authorities (NRAs) and vaccine manufacturers on clinical evaluation of vaccines was held from 17 to 18 July 2014, to review key scientific challenges that regulators have been facing since the establishment of the WHO Guidelines on Clinical Evaluation of Vaccines. The guidelines, adopted by the WHO Expert Committee on Biological Standardization (ECBS) in 2001, have served as the basis for setting or updating national requirements for the evaluation and licensing of a broad range of vaccines as well as for WHO vaccine prequalification. Regulators from Australia, Brazil, China, Canada, Germany, India, Republic of Korea, South Africa, United States of America and the United Kingdom were represented. The International Federation for Pharmaceutical Manufacturers' Association (IFPMA) and the Developing Country Vaccine Manufacturers' Network (DCVMN) provided industry representation.

The consultation concluded that the guidelines should be revised to address issues that were raised in the context of vaccines that were the subject of clinical development in the past decade. Although the current guidelines have served well over time, it was recognized that an update would further increase their utility and would help regulators, manufacturers, vaccine developers and academia to respond to the challenging questions regarding the safety, immunogenicity, efficacy and effectiveness of vaccines intended for global use. A summary of the main outcomes of the consultation and proposals for the next steps regarding the guidelines and beyond are provided in this report.

1. Background information

The WHO Guidelines on Clinical Evaluation of Vaccines were adopted by the WHO Expert Committee on Biological Standardization (ECBS) in 2001 and published in the WHO Technical Report Series (TRS) 924, Annex 1. The guidelines provide a number of guiding principles for regulatory review of clinical data and it has served as a basis for setting or updating national requirements for the evaluation and licensing of a broad range of vaccines as well as for WHO vaccine prequalification.

Among other messages that the WHO Guidelines have conveyed since their establishment, is the role of National Regulatory Authorities (NRAs), the importance of clearly defining national requirements and early dialogue between vaccine manufacturers and regulators were emphasized as key elements of effective regulation.

2. Aim of the WHO consultation in July 2014

A WHO consultation on guidelines for NRAs and vaccine manufacturers on clinical evaluation of vaccines was held from 17 to 18 July 2014, to review key scientific challenges that regulators have been facing since the establishment of the WHO Guidelines on Clinical Evaluation of Vaccines. The consultation aimed to identify a need for updating the guidelines and to also reach a consensus on the key issues that need to be addressed in the revision. This is the first step in initiating a broader consultation on this topic with experts from WHO Member States.

The consultation was organized by the WHO Technology, Norms and Standards team of the Department of Essential Medicines and Health (EMP/RHT/TSN) and the Initiative for Vaccine Research (IVR/IVB) team. Dr James Southern chaired the consultation and Dr Rebecca Sheets served as the Rapporteur.

Regulators, manufacturers, clinical researchers and academic investigators from Australia, Brazil, China, Canada, Germany, India, Republic of Korea, South Africa, United States of America and the United Kingdom were represented. The International Federation for

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Pharmaceutical Manufacturers' Association (IFPMA) and the Developing Country Vaccine Manufacturers' Network (DCVMN) provided industry representation.

3. Challenging issues in clinical evaluation of vaccines from a perspective of regulators and manufacturers

As part of the preparation for the consultation, participants were invited by WHO to review the guidelines on clinical evaluation of vaccines and to prepare some comments and proposals for its revision.

Regulators from several countries presented their answers to the following three questions regarding the situation in their own country:

- Which WHO or other international guidelines are actually used?
- What is implemented into local guidelines/regulations?
- What are additional topics needed in the revision of this WHO guideline?

3.1. Regulators (Australia, Brazil, China, India, Republic of Korea, South Africa)

Presentations were provided by the NRA representatives from the countries listed above, although other NRAs were present and provided comments and discussion. In general, a number of WHO guidelines, including the Guidelines on Clinical Evaluation of Vaccines are used by NRAs—either adopted or adapted as their own local guidelines or incorporated by reference or indirectly incorporated into their regulations or laws. For example, Brazil endorses the PANDRH document on Licensing of Vaccines in the Americas, which refers to the WHO Guidelines on Clinical Evaluation of Vaccines.

Other common themes raised by the NRAs were to provide clarity regarding the use of the Brighton Collaboration diagnostic and case definitions vs. the use of mEDRA coding in reporting of adverse events (AEs); clarity on the requirement for and timing of clinical studies to support lot-to-lot consistency; clarity on which aspects of the WHO guidelines pertained primarily to novel or new vaccines (containing components that have not been used in previously licensed or registered vaccines) and those applicable to follow-on vaccines; vaccines that have been tech-transferred to a new in-country manufacturer; or vaccines formulated from components (bulks) already included in existing licensed or registered vaccines. The latter categories of vaccines would not generally need the same extensive clinical trial programme that completely novel or new vaccines would require. However, the current guidelines are silent in that regard and may be misinterpreted to suggest that all types of vaccines, no matter the degree of pre-existing data on the same or similar immunogens contained in existing vaccines, would need the same clinical development programme, which is not the case.

The consultation recognized that the revision of the guidelines is an important step in assisting WHO Member States in developing or updating national requirements for clinical evaluation of vaccines. However, these guidelines are not expected to resolve all practical issues and therefore, it was also considered what should be provided as additional tools in assisting regulators on that matter. As an example, WHO activities in facilitating implementation of guiding principles into regulatory and manufacturing practice were recognized as an essential tool towards better regulatory preparedness and convergence. Furthermore, requests were made for some training materials that need to be developed or updated in order to provide tools for building expertise for clinical evaluation in developing countries. A need for scientific advice as a complementary tool to facilitate application of guiding principles in specific cases was identified. The utility of regional expertise and collaboration within such groups as the African Vaccine Regulatory Forum (AVAREF) and the Developing Country Vaccine Regulators' Network (DCVRN) was duly recognized.

3.2. Vaccine developers and manufacturers (IFPMA & DCVMN)

Representatives from IFPMA and DCVMN provided their input on the issues that need to be updated or amended in the existing guidelines. Their feedback was in-line with comments and discussion of other presenters and they provided some practical and valuable feedback on the impact, sometimes unintended by the original authors, of some of the language or lack of clarity in the guidelines—which can be amended in the revision to improve understanding by all parties. It was agreed that their suggestions would improve the guidelines for all users. The importance of applying principles on a case-by-case basis was discussed. For instance, it is stated in the guidelines that Phase I is "primarily" intended for safety evaluation but it does not mean that immunogenicity should not be done in that study, when appropriate. A need for flexible approach in a given situation is essential for science based regulation.

4. Revision of WHO Guidelines on Clinical Evaluation of Vaccines

It was agreed that the guidelines should be revised and updated. Below is a summary of the main outcomes of the discussion and specific agreements regarding purpose, scope, etc.

4.1. Main outcomes of discussion

Many issues were discussed and the outcomes are described below thematically. One issue not covered in the current guidelines, but important, is that of conducting human challenge studies and their potential role in vaccine development. Also, there are some safety considerations related to challenge trials that need to be considered in the revision. The experience gained with more than ten pathogens clearly show that these studies provide important information about the disease as well as for vaccines under development, notably *P. falciparum* malaria, typhoid and cholera. Some of the lessons learned, in particular, in low- and middle-income countries, may serve as a starting point for defining regulatory considerations for these studies. But there are many other issues that would be more appropriate for vaccine developers and therefore, would most likely require a separate document.

In addition, it was agreed to address some special considerations for combined vaccines apart from DT-based combinations. The need for separate guidance on special considerations for adjuvanted vaccines was recognized, as there are WHO Guidelines on Nonclinical Evaluation of Adjuvants and Adjuvanted Vaccines, but no specific clinical guidelines on the same.

One of the topics of importance for global immunization practice which goes beyond regulatory issues is that of maternal immunization. Pregnant women may be vaccinated for different purposes; either to protect themselves where pregnancy is a specific risk group for a particular disease, or to protect their neonate, once born, for example, tetanus, influenza and pertussis. Given that pregnant women are increasingly recognized as one of the priority target groups for immunization in some vaccine areas, the issue of maternal immunization was proposed as an appendix to the revised guidelines. The intention is to provide some guiding principles for studies carried out on pregnant women and women during the lactation period on the one hand and to elaborate on maternal immunization intended to protect infants in the cases of, for

example, tetanus, pertussis, influenza, RSV, Group B Streptococcus and CMV.

Several aspects of early clinical trials were also discussed. While experimental medicines and translational research have expanded in scope since the publication of the current guidelines, it was felt that it may still be premature to provide specific guidelines for clinical trials performed for the purpose of experimental medicines rather than specific product development. However, translational research sometimes transitions to product development. Therefore, it would be appropriate to discuss this issue in the context of the recently appointed WHO Product Development for Vaccines Advisory Committee. Acknowledgement, however, that trials may be performed for the purposes of experimental medicines and/or translation research should be noted in these guidelines.

The experience gained with adaptive clinical trial designs was discussed in the context of regulatory considerations and it was agreed to provide a brief explanation on the characteristics of such trials, as there may be confusion. For instance, predefined criteria for expected changes to clinical trial conduct were described as a flexible approach which is intended to facilitate development of novel vaccines in certain cases. One of the difficulties is that the statistical analysis of the data from an adaptive trial design is exceedingly complex and should take into account these prospectively planned changes and their impact on the power of the study. Since the use of adaptive trial design to support vaccine development is still a concept under development from the regulatory perspective, it would be sufficient to provide brief information, cite current literature that elaborates in much greater detail and maybe provide some examples on the appropriate uses of such studies.

It was noted that preliminary efficacy studies, often called Phase IIb studies, have been a major feature of several clinical development programmes (for example, malaria, dengue, HIV, tuberculosis, HPV). It was agreed that the value of Phase IIb studies as well as the situations where such studies may be needed should be described in a reasonably concise way. It was also discussed that the nomenclature of Phases I, Ia and Ib, Phases II, IIa and IIb and Phase III can become semantics and to describe the intent and purpose of the trial as a primary defining characteristic of where it fits into the overall clinical development programme should be clarified in the revision of the guidelines.

An additional key issue identified to be included in the revision of the guidelines was a need to provide greater clarity on the "sliding scale" or progressive nature of the rigour of expectations for product quality; how nonclinical studies inform clinical trials and rigour of expectations for assays (both quality and clinical) as clinical trials progress in all Phases. Specifically, expectations that at Phase I (particularly, first-in-human studies) there will be lot-to-lot consistency; process validation; stringent lot release criteria; all nonclinical studies completed and immunological or clinical endpoint assays validated; is unrealistic and inappropriate. While such expectations are realistic at or during Phase III (or pivotal clinical trials), they are not at Phase I. This is not to suggest that scientific rigour and good practices should not be implemented by Phase I, but rather that not all facets will be ready at such an early stage of product development, since the purpose of product and clinical development is to refine and improve all of these things so that by the time of commercialization, an optimized, validated, consistent product may be launched.

Increasingly, vaccines are being developed that will likely have a great impact on public health, but which will not achieve nearly the degree of vaccine efficacy (VE) seen with legacy vaccines like polio or measles. New vaccines of modest efficacy may help to curb disease burden where it is high, but these places may be exactly those where the regulatory experience has mainly been gained with vaccines of extremely high efficacy. Thus, some discussion on evaluating the risk and benefit of a vaccine based on the level of efficacy shown, whatever that level may be, is needed in the guidelines. Understanding the power of the statistics and what they demonstrate and the potential need for more than one concordant study to gain confidence that a modestly efficacious vaccine can actually be effective is important.

Another issue that garnered significant discussion was that of the requirement for local, in-country data and the reluctance to accept foreign data for the purposes of licensure (or even initiation of advanced clinical trials) in any particular country. The need to consider study designs that permit efficient capture of data in geographically disperse or genetically diverse populations to give sufficient power to permit countries to accept foreign data was recognized and should be discussed in the revised guidelines. The intent is that the perceived need to require local data should not deter the introduction of efficacious vaccines for populations of greatest need at the earliest appropriate moment and where possible, to avoid conduct of small studies with no valid scientific purpose.

Finally, there was consideration on better ways to describe the statistics of sample sizes needed to acquire safety data. The current guidelines have numbers such as "300" or "5000," which while they have a statistical basis—that basis is not described and is not always appropriate, leading to potential inflexibility. Rather, discussion should be on the need to statistically calculate a sample size that will permit collection of safety data that will permit identification of common (1/100) and uncommon (for example, 1/1000) AEs. Also, there needs to be a recognition and acknowledgement that not all safety issues may be fully characterized at the time of licensure and thus, to discuss when there is a need for post-approval collection of safety and in fact, effectiveness, data, among other issues that can only be addressed once a vaccine is in more wide-spread use.

4.2. Consensus statement on key issues to be addressed

4.2.1. Purpose of the guidelines

It was agreed that the purpose of the guidelines are to support both clinical trial approval and licensure or registration of vaccines and not just solely the latter. It was also agreed that the guidelines are meant to inform not only regulators, but also industry and researchers about regulatory expectations, although the main purpose of the guidelines are to aid regulators in their clinical evaluation of vaccines.

4.2.2. Scope

It was agreed that the scope of the guidelines would be prophylactic vaccines and would not tackle therapeutic vaccines for which clinical development could be quite different. Also, many aspects that are in the current guidelines are no longer appropriate for the scope of this document given that there are newer WHO guidelines that cover those specific topics, such as nonclinical evaluation and aspects of good clinical practices (GCP), in particular ethical considerations. While ethical considerations that are relevant to clinical evaluation or clinical trial design will necessarily be discussed within appropriate sections of the revised guidelines (for example, the use of a placebo control group or choice of control group(s)), a separate section on ethical considerations will no longer appear, as this would have the potential to conflict with the WHO guidelines on GCP and for ethics review committees and those documents should supersede.

4.2.3. Additional points

Additional points to those raised in the section on *Main Outcomes of the Discussion* are:

- the concept of heterologous prime-boost regimens;
- what to do in the case of hyporesponsiveness to vaccination in certain populations;
- how to identify and define immune correlates of protection, including threshold values and what to avoid in order to not misuse these;
- vaccines that may have short durability of protection;
- concern for biocreep or immunological "creep" when selecting a choice of control group;
- size of safety databases by sub-groups (for example, age);
- situations in which age de-escalation studies may be inappropriate;
- use of a comparator arm that may not be licensed in the country where the trial is being performed or which may be of unknown efficacy;
- use of live or replication-incompetent viral vectors as vaccines for diseases other than that caused by the virus used as the vector;
- clarifying roles of the sponsor vs. public health authorities in post-approval data collection and analysis;
- concomitant use of vaccines
- evaluating the need for booster doses in the faces of waning immunity; and
- discerning whether waning immunity correlates with waning efficacy or not, among others.

4.2.4. Updates

Sections that require updating were discussed and those aspects where additional clarity or revision is needed will be addressed by the drafting group. Some of these aspects are mentioned above in the section on the *Main Outcomes of the Discussion*. Also, it was noted that the Glossary requires updating and definitions provided for several keywords (for example, licensure, registration and lot consistency are among others).

4.2.5. Other changes

It was agreed that the Table of Contents will be revised and that certain sections will be deleted and the information in those sections placed into other appropriate places or deleted altogether as they are covered by other, newer WHO Guidelines—(for example, the sections on *General Remarks*, *Methodological Considerations*, *Statistical Considerations* and *Ethical Considerations*). It was agreed that whatever decision is taken concerning the Table of Contents, it will always be made clear how different principles and considerations apply at different stages of development, and this must be made clear in the drafting of the revised guidelines. It may be appropriate to include numbered subsections on early and late stage developmental considerations for each content area, where appropriate.

5. Conclusions and pathway forward

It was concluded that there were very few issues in the current guidelines that were altogether out-of-date. Nonetheless, a number of points were proposed to be included as additional issues to be addressed and that the organization of the guidelines could be improved to reduce redundancy and improve flow of information in a more logical order. It was universally agreed that the existing guidelines have been of great value to regulators and industry alike, as well as researchers. The consultation concluded with agreement, that the guidelines should be revised to address issues that were raised in the context of vaccines that were the subject of clinical development in the past decade. Although the current guidelines have served well over time, it was recognized that an update would further increase their utility and would help regulators, manufacturers, vaccine developers and academia to understand expectations in terms of safety, immunogenicity, efficacy and effectiveness data that are needed for vaccines intended for global use.

5.1. Plan for revision of the guidelines

A drafting group has been identified and will initiate writing of the revision of the guidelines with plans to complete this by the end of 2014 or in early 2015. The first rough draft of the revision will be circulated to participants who took part in the consultation and other critical reviewers to improve it before circulating it for public comment. Revisions will be made by the drafting group before the guidelines are circulated for public comment. It is likely that at least three rounds of circulation to critical reviewers and public comment will be undertaken before a final draft will be submitted to the ECBS for review and adoption at the next meeting to be held in October 2015.

5.2. Beyond the guidelines

The consultation did recognize that the guidelines can only go so far in supporting capacity building of developing country regulators and assuring that vaccines are licensed or registered and access given to the populations of greatest need in as rapid a fashion as prudent and appropriate. Some of the additional needs for these goals were discussed briefly:

5.2.1. Training materials and e-learning tools needed

The guidelines by their very nature, must be written generically and flexibly and not all aspects will apply in all circumstances and situations. Training and experience is also needed to know when to apply which aspects and specific examples and case studies can aid in such training. Thus, to supplement what the guidelines cannot do, development of training materials and e-learning tools were requested by some NRAs present at the consultation. Access to scientific expert advice in some manner to assist NRAs in their review process was also requested.

5.2.2. Implementation of guidelines into practice

To be truly effective, the guidelines need to be implemented into practice. To facilitate this, WHO plans to hold one or more implementation workshops once the ECBS has adopted the revised guidelines. Further discussion on implementation may occur at later stages of development of the revision.

5.2.3. Vaccine Trial Registries

Vaccine Trial Registries as international databases provide valuable information on the latest clinical trials conducted for vaccines of interest. Also recognized was the importance of ensuring reporting of important clinical trial results in a reasonable timeframe and some recent literature that suggests that as many as 30% of completed trials are not reported within two years or even up to six years after completion (Manzoli et al., BMJ 2014;348:g3058). Providing a clear definition on when a trial is considered completed might assist in this regard, as some sponsors will not consider a trial completed even long after the last study visit and primary or even secondary analyses, if there continues to be some type of longer-term follow-up going on in the study (for example, yearly phone calls for up to five years after the last study injection).

Disclaimer

This article contains the views of the authors and does not necessarily represent the decisions or the stated policy of the World Health Organization.

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